Active

Project #: E-19-X13 Cost share #: Rev #: 1
Center # : 10/24-6-R7106-3A0 Center shr #: OCA file #:
Work type : RES
Contract#: 5 R01 HL45485-03 Mod #: BR DTD 3/31/93 Document : GRANT
Prime #: Contract entity: GTRC

Subprojects ? : N CFDA:
Main project #: PE #: N/A

Project unit: CHEM ENGR Unit code: 02.010.114
Project director(s):
YOGANATHAN A P CHEM ENGR (404)894-2849

Sponsor/division names: DHHS/PHS/NIH / NATL INSTITUTES OF HEALTH
Sponsor/division codes: 108 / 001

Award period: 930101 to 931231 (performance) 940331 (reports)

Sponsor amount	New this change	Total to date
Contract value	2,490.40	126,975.40
Funded	2,490.40	126,975.40
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: QUANTITATION OF VALVULAR REGURGITATION: AN IN VITRO STUDY

PROJECT ADMINISTRATION DATA

OCA contact: Kathleen R. Ehlinger 894-4820

Sponsor technical contact	Sponsor issuing office
DR. ISABELLA Y. LIANG	J. KEVIN KEATING
(301)496-1081	(301)496-7536
NATIONAL INSTITUTES OF HEALTH	NATIONAL INSTITUES OF HEALTH
NHLB INSTITUTE	NHLB INSTITUTE
CARDIAC DISEASES BRANCH	GRANTS OPERATION BRANCH
FEDERAL BUILDING, ROOM 3C06	FEDERAL BUILDING
BETHESDA, MD 20893	BETHESDA, MD. 20893

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A NIH supplemental sheet
Equipment title vests with: Sponsor GIT X

Administrative comments -
ISSUED TO CARRY FORWARD UNEXPENDED FUNDS FROM E-19-606 & E-19-685. UNEXPENDED FUNDS EQUAL $2,490.40 TOTAL.

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 01/26/94

Project No. E-19-X13_____ Center No. 10/24-6-R7106-3A0_

Project Director YOGANATHAN A P_____ School/Lab CHEM ENGR_____

Sponsor DHHS/PHS/NIH/NATL INSTITUTES OF HEALTH_____

Contract/Grant No. 5 R01 HL45485-03_____ Contract Entity GTRC

Prime Contract No. _____

Title QUANTITATION OF VALVULAR REGURGITATION: AN IN VITRO STUDY_____

Effective Completion Date 931231 (Performance) 940331 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	N	_____
Final Report of Inventions and/or Subcontracts	N	_____
Government Property Inventory & Related Certificate	N	_____
Classified Material Certificate	N	_____
Release and Assignment	N	_____
Other _____	N	_____

CommentsCONTINUED BY E-19-X41._____

_____

Subproject Under Main Project No. _____

Continues Project No. _____

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other CARL BAXTER-FMD_____	Y
_____	N

GEORGIA TECH RESEARCH CORPORATION

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION
PROGRAM INITIATION DIVISION
ATLANTA, GEORGIA 30332-0420
USA

Telex: 542507 GTRC OCA ATL
Fax: (404) 894-6956

Phone: (404) 894-4817

Refer to: JLG/02.108.001.94.005

13 October 1993

National Institutes of Health
NHLBI-DEA
Grants Operations Branch
Westwood Building, Room 4A09A
Bethesda, Maryland 20892

Attention: Dr. Isabella Liang

Subject: Research Proposal Entitled, "Quantitation of Valvular Regurgitation: An In Vitro Study"

Dear Dr. Liang:

GEORGIA TECH RESEARCH CORPORATION is pleased to submit for your consideration the subject proposal prepared by Dr. Ajit P. Yoganathan, School of Chemical Engineering, Georgia Institute of Technology.

A description of the research program, the time required and estimated cost are included in the proposal. Should additional information be desired, please do not hesitate to contact Dr. Yoganathan at 404-894-2849 regarding technical matters or the undersigned at 404/894-4817 for administrative matters.

In the event of an award, we propose that the work be authorized by a grant continuation drawn in the name of the GEORGIA TECH RESEARCH CORPORATION.

We appreciate the opportunity to submit this proposal and look forward to hearing from you soon.

Sincerely,

Janis L. Goddard
Contracting Officer

JG/pw

Addressee: Original and five copies
Enclosure: Proposal - Original and five copies

SAT

Form approved through 6/30/94
OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HUM... SERVICES
PUBLIC HEALTH SERVICE

APPLICATION FOR CONTINUATION GRANT

REVIEW GROUP	TYPE	AC	Y	GRANT NUMBER
(AHR-M1)	5	RO1		HL45485-04

TOTAL PROJECT PERIOD
From: 01/01/91 Through: 12/31/94

REQUESTED BUDGET PERIOD
From: 01/01/94 Through: 12/31/94

To be verified by applicant. Check information in items 1 through 6. If incorrect, furnish correct information in item 13.

1. TITLE OF PROJECT

QUANTITATION OF VALVULAR REGURGITATION AN IN VITRO STUDY

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Name and address, street, city, state, zip code)*

YOGANATHAN, AJIT P
GEORGIA INST OF TECHNOLOGY
SCHOOL OF CHEMICAL ENGINEERING

4. APPLICANT ORGANIZATION *(Name and address, street, city, state, zip code)*

GEORGIA INST OF TECHNOLOGY
225 NORTH AVENUE
ATLANTA, GA 30332

BITNET/INTERNET ADDRESS

5. ENTITY IDENTIFICATION NUMBER
15806031464A1

2b. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
SCHOOL OF CHEMICAL ENGINEERING

2c. MAJOR SUBDIVISION
COLLEGE OF ENGINEERING

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT *(See instructions)*
20 OTHER

6. TITLE AND ADDRESS OF ADMINISTRATIVE OFFICIAL
CONTRACTING OFFICER
CENTENNIAL RESEARCH BLDG
ROOM 246
GEORGIA INST OF TECHNOLOGY
ATLANTA, GA 30332-0420

BITNET/INTERNET ADDRESS

Complete the following *(see instructions)*

7. HUMAN SUBJECTS — If "YES" exemption no. or IRB approval date — 4b. Assurance of compliance no.
[X] 7a. NO [ ] YES

8. VERTEBRATE ANIMALS — If "YES," IACUC approval date — 8b. Animal welfare assurance no.
[X] 8a. NO [ ] YES

9. PERFORMANCE SITE(S) *(Organizations and addresses)*

Cardiovascular Fluid Mechanics Laboratory
School of Chemical Engineering
Georgia Institute of Technology
Atlanta, GA 30332-0100

10. COSTS REQUESTED FOR NEXT BUDGET PERIOD
10a. DIRECT $ 95,051 10b. TOTAL $ 130,220

11. INVENTIONS AND PATENTS *(See instructions)*
[X] NO [ ] YES If "YES," [ ] Previously reported [ ] Not previously reported

TELEPHONE AND FAX INFORMATION

	AREA CODE	TELEPHONE NO. AND FAX NO.
12a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Item 2a)*	404 404	894-2849 894-2291
12b. NAME OF ADMINISTRATIVE OFFICIAL *(Item 6)* Janis L. Goddard	404 404	894-4817 894-6956
12c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 15)* Christopher E. D'Urbano Contracting Officer		

BITNET/INTERNET ADDRESS

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWERS APPLY.

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).	SIGNATURE OF PERSON NAMED IN 2a *(In ink. "Per" signature not acceptable.)*	DATE 10/8/93
15. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79)	SIGNATURE OF PERSON NAMED IN 12c *(In ink. "Per" signature not acceptable.)*	DATE 10/13/93

DETAILED BUDGET FOR NEXT BUDGET PERIOD DIRECT COSTS ONLY	FROM 01/01/94	THROUGH 12/31/94	GRANT NUMBER HL 45485-04

PERSONNEL (Applicant organization only) NAME	ROLE ON PROJECT	TYPE APPT. (months)	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED (Omit cents) SALARY REQUESTED	FRINGE BENEFITS	TOTALS
A. P. Yoganathan	PI	12	25	92000	23000	5773	28773
Graduate Research Assistant	Grad Student	12	100				17000
Graduate Research Assistant	Grad Student	12	100				17000
Secretary*		12	10	27000	27000	678	3378
SUBTOTALS →							66151

CONSULTANT COSTS			
Dr. R. A. Levine, 20 days (@ $325 per day)			6500
5 day visit to Georgia Tech (4 times per year) - Travel Expenses			5500
EQUIPMENT (Itemize)			
XC:			
E'11-X41			0
SUPPLIES (Itemize by category)			
Photographic (polaroid, regular film & video tape)		2500	
Mechanical (For in vitro models and pulse duplicator system)		2500	
Electrical " " " " " " " "		1000	
Chemical " " " " " " " "		1000	
			7000
TRAVEL			2500
PATIENT CARE COSTS — INPATIENT			
PATIENT CARE COSTS — OUTPATIENT			
ALTERATIONS AND RENOVATIONS (Itemize by category)			
OTHER EXPENSES (Itemize by category)			
Service Contract on Vingmed SD-100 ultrasound Doppler system		4400	
Machine shop charges for model building*		3000	7400
SUBTOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD			95051
CONSORTIUM/CONTRACTUAL COSTS			
DIRECT COSTS $ _____	TOTAL →		0
INDIRECT COSTS $			
TOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD (Enter on Page 1, Item 10a) →		$ 95051	

BUDGET JUSTIFICATION	C IT NUMBER HL 45485-04

SUPPLEMENTAL INFORMATION REGARDING *ITEMS* IN THE PROPOSED BUDGET FOR THE NEXT PERIOD WHICH REQUIRE EXPLANATION OR JUSTIFICATION. *(See instructions)*

PERSONNEL

The key personnel listed are those as approved in the original proposal. The personnel budget is the same as that recommended by the Review Group. The salary increase for the PI and the Graduate Research Assistants are in line with Georgia Tech's salary increases. The GRAs are pursuing their Ph.D. degrees based on the research they are conducting on this project.

CONSULTANT

These costs are identical to those approved by the Review Group. The consultant, Dr. R. A. Levine, is vital to the success of the project.

SUPPLIES

Per the original proposal budget, a variety of mechanical, electrical, chemical and photographic supplies are required for the proposed work.

TRAVEL

To attend and present the results of the research at two engineering and biomedical meetings - per original proposal budget.

OTHER EXPENSES

The service contract on the Vingmed SD-100 ultrasound Doppler system - per original proposal budget.

*ADDITIONAL ITEMS ADDED TO BUDGET

Secretarial time charges and machine shop charges at Georgia Tech in the past have been paid for from overhead funds. However, with the new rules by OMB on overhead cap, such items have to be charged directly to the project. The secretary's time (10%) plus machine shop charges (based on current usage) have been included in the new budget and are clearly justified. The lack of these funds ($63378) will slow down the project.

CURRENT BUDGET PERIOD	FROM 01/01/93	THROUGH 12/31/93

The following pertains to your CURRENT PHS budget. This information may be used in determining the amount of support for the NEXT budget period.

A. CURRENT BUDGET	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (1)	ESTIMATED UNOBLIGATED BALANCE (2)	EXPLAIN ANY SIGNIFICANT ESTIMATED UNOBLIGATED BALANCE IN COLUMN 2 (3)
TOTAL DIRECT COSTS	85911	0	
INDIRECT COSTS *(As provided)*	38574	0	
TOTALS →	124485	0	

OTHL SUPPORT *(Use continuation pages if necessary)*	GRA NUMBER HL 45485-04

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to significant delays in the review and/or funding of the application.

Other support is defined as all funds or resources, whether Federal, non-Federal, or institutional, available to the principal investigator/program director (and other key personnel named in the application) in direct support of their research endeavors through research or training grants, cooperative agreements, contracts, fellowships, gifts, prizes, and other means.

Reporting requirements are: For each of the key personnel, describe (1) all currently *active* support and (2) all applications and proposals *pending* review or award, whether related to this application or not. If the support is part of a larger project, identify the principal investigator/program director and provide the data for the relevant subproject(s). If an individual has no active or pending support, check "None." Use continuation pages as needed to provide the required information in the *format* as shown below. Key personnel are defined as all individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project.

Name Ajit P. Yoganathan Active X Pending _____ None _____

a. Source and identifying no. None P.I. Ajit P. Yoganathan

Title Fellowships in Cardiovascular Fluid Mechanics

b. Your role on project PI % Effort 0

c. Dates and costs of entire project 7/01/93 - 6/30/94 $50000

d. Dates and costs of current year 7/01/93 - 6/30/94 $50000

e. Specific aims of project Fellowship funds from industrial sources to support graduate students and post doctoral research fellows conducting research in the area of cardiovascular fluid mechanics.

f. Describe scientific and budgetary overlap None

g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.)

OTHER SUPPORT *(Use continuation pages if necessary)*	GR. NUMBER HL45485-04

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to significant delays in the review and/or funding of the application.

Other support is defined as all funds or resources, whether Federal, non-Federal, or institutional, available to the principal investigator/program director (and other key personnel named in the application) in direct support of their research endeavors through research or training grants, cooperative agreements, contracts, fellowships, gifts, prizes, and other means.

Reporting requirements are: For each of the key personnel, describe (1) all currently ***active*** support and (2) all applications and proposals ***pending*** review or award, whether related to this application or not. If the support is part of a larger project, identify the principal investigator/program director and provide the data for the relevant subproject(s). If an individual has no active or pending support, check "None." Use continuation pages as needed to provide the required information in the ***format*** as shown below. Key personnel are defined as all individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project.

Name Ajit P. Yoganathan Active _____ Pending X None _____

a. Source and identifying no. NIH P.I. Ajit P. Yoganathan

Title Fluid Mechanics of the Mitral Valve: In Vitro Studies

b. Your role on project Principal Investigator % Effort 25

c. Dates and costs of entire project 4/1/94 - 3/31/97 $487,220

d. Dates and costs of current year 4/1/94 - 3/31/95 $161,905

e. Specific aims of project To establish the mechanics of normal and fixed mitral valves in well controlled in vitro experiments. To investigate the effects of structural modifications to the mitral valve complex. To investigate the effect and interaction of the mitral valve complex with prosthetic heart valves.

f. Describe scientific and budgetary overlap None

g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.)

OTH' 'UPPORT *(Use continuation pages if necessary)*	GRA 'UMBER HL 45485-04

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to significant delays in the review and/or funding of the application.

Other support is defined as all funds or resources, whether Federal, non-Federal, or institutional, available to the principal investigator/program director (and other key personnel named in the application) in direct support of their research endeavors through research or training grants, cooperative agreements, contracts, fellowships, gifts, prizes, and other means.

Reporting requirements are: For each of the key personnel, describe (1) all currently *active* support and (2) all applications and proposals *pending* review or award, whether related to this application or not. If the support is part of a larger project, identify the principal investigator/program director and provide the data for the relevant subproject(s). If an individual has no active or pending support, check "None." Use continuation pages as needed to provide the required information in the *format* as shown below. Key personnel are defined as all individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project.

Name Ajit P. Yoganathan Active _____ Pending X None _____

a. Source and identifying no. NIH P.I. Carol L. Lucas

Title Fluid Dynamics of Right Heart - Bypass Options

b. Your role on project PI of Subcontract % Effort 25

c. Dates and costs of entire project 7/01/94 - 6/30/98 $414152 (subcontract)

d. Dates and costs of current year 7/01/94 - 6/30/95 $96112 (subcontract)

e Specific aims of project The goals of the study are to: (1) evaluate the fluid dynamics associated with surgical repair options for congenital defects interrupting or severely impairing the pulmonary circulation--to examine perioperative results and to project the impact of growth on those results; and (2) develop computational techniques that facilitate evaluation of surgical materials and procedures--to provide a computer aided design (CAD) tool for previewing repair options.

f. Describe scientific and budgetary overlap None

g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.)

None

PROGRESS REPORT SUMMARY	GF NUMBER HL 45485-04	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR Ajit P. Yoganathan	PERIOD COVERED BY THIS REPORT FROM	THROUGH
APPLICANT ORGANIZATION Georgia Institute of Technology	01/01/93	12/31/93

TITLE OF PROJECT *(Repeat title shown in item 1 on first page)*
Quantitation of Valvular Regurgitation: An In Vitro Study
(SEE INSTRUCTIONS)

1. Specific Aims

The goals of this proposal are three-fold. **First**, the study will address the hypothesis that equations can be derived from basic fluid mechanic principles to quantify regurgitant volume using quantities that can be directly measured by Doppler. **Second**, these basic physical principles can be used to interpret color flow mapping variability related to regurgitant jet behavior in the presence of solid structures or interrupting flows. **Third**, additional variability inherent to measurement technique (i.e. instrument settings) will be addressed.

To achieve these objectives, the following specific aims are proposed: 1) to derive equations from the principles of turbulent jet flow and conservation of mass which provide orifice flow rate, and therefore regurgitant volume, as a function of Doppler measurable quantities; 2) in *in vitro* models, to test the accuracy of the equations in predicting actual regurgitant volume; 3) to define in an *in vitro* model, the relationship between regurgitant flow, and spatial characteristics of the color flow jet, namely, jet length, width, area, and volume; 4) in *in vitro* models, to address the variability in these relationships due to machine settings, driving pressure, and physiologically observed jet flow phenomena, namely, the Coanda effect, impingement, counterflow, and coflow; and 5) to investigate the applicability of the quantitation techniques to various designs of heart valve prostheses.

These comprehensive studies are performed *in vitro* in order to allow precise and independent control of all variables. *In vivo* studies, while providing realistic environments, do not generally allow independent control of variables such as required for such fundamental studies. Careful design of flow models provides semi-realistic environments, while allowing dependent control.

2. Studies and Results

A. EFFECTS OF CONFINED AND IMPINGING REGURGITANT JETS

Methods have recently been developed for noninvasive quantification of valvular regurgitant flow rate (Q_{op}) based on conservation of momentum within free turbulent jets and the resulting decay of peak centerline velocities (U_{mp}) distal to the orifice. Before clinical implementation, however, the method must account for realistic environments in which jets are limited axially (impinging on distal walls), confined laterally or both, causing more rapid velocity decay. We proposed that accurate results could be achieved for such jets using a technique based on the continuity principle coupled with a dimensional analysis involving factory affecting U_{mp}: receiving chamber diameter (D_c) orifice-to-end wall distance (H), distance from the orifice, peak orifice velocity (U_{op}) and orifice diameter (D_o). The purpose of this study was to validate this method in vitro, over a wide range of heart rates (HR), U_{op}, and H. Physiologic pulsatile flows were pumped through circular orifices (D_o=2,4 mm) at 70 - 150 beats/min in two receiving chambers (D_c=51, 88 mm); at each HR, U_{op} was varied from 2 - 5 m/s. H varied from 30 - 93 mm. U_{mp} was measured by pulsed Doppler ultrasound over multiple beats and Q_{op} calculated. Predicted Q_{op} agreed well with actual values by electromagnetic flow probe, independent of HR. For example, for D_c=51 mm, H= 66 mm, the regression for Q_{op} was y=0.97x-0.21 (r=0.99). For D_c=51 mm, H=30 mm, the regression was y= 1.01x+0.13 (r=0.99). For a wide range of

geometries confining jets axially and laterally, Q_{op} can be accurately predicted in vitro from velocities that can be directly measured by conventional Doppler.

B. INSTRUMENTATION FACTORS IN ASSESSING REGURGITANT JET SIZE

Color Doppler (CD) jet flow area (CDA) continues to be used as the primary noninvasive marker of the severity of valvular regurgitation (VR) and the transesophageal approach (TEE) has aided visualization of CDA in prosthetic valves. It has been shown that CDA varies significantly between transthoracic and TEE views within a given instrument. In order to define useful thresholds of severity of VR, it is critical to examine the variability between different instruments and between instrument settings for the same flow. This study therefore addressed the effect of instrument settings and intermachine variability in a comprehensive manner using six commonly used TEE instruments. Commercially available CD instruments by Acuson, Aloka, ATL, HP, Toshiba and VingMed with 5 MHz transesophageal probes were used to image pulsatile jet flow through a 5 mm orifice using a blood analog fluid. For all six machines studied, a reduction in Nyquist Limit (0.46 - 0.32 m/s) resulted in an increase in CDA (8.82-18.10 cm^2) ($p=0.001$). Nyquist limit should not in principle affect CDA, and these changes are explained by changes in wall filter. With other settings constant, increasing sector angle (45°-90°) produced larger jets (13.23 - 18.44 cm^2) due to lateral resolutions effects ($p=0.01$). Virtually identical setting combinations showed intermachine differences as high as 57%. Instrument settings cause significant variations in CDA for constant flow conditions and so must be annotated and recorded. Limited setting choices and arbitrary annotation prohibits extrapolation of assessment techniques between instruments.

C. PROSTHETIC VALVE STUDIES

A theoretical treatment using turbulent jet theory has yielded a new equation for predicting regurgitant flow through bileaflet heart valve prostheses, the most commonly implanted mechanical valve design. Previously reported techniques assuming an axisymmetric jet are not applicable to the slot-like orifices presented in these valves. The equations were therefore rederived in the context of the prosthetic valve geometry. The purpose of this study was to develop such a method and demonstrate its applicability in principle by using in vitro models. The method was validated under both steady and pulsatile flow conditions. Having derived a method geometrically specific to the orifices presented in bileaflet mechanical heart valves. It should be applicable from patient to patient due to the rigid nature of the valve. These idealized in vitro studies, along with the accompanying theoretical derivation, will guide implementation in the clinical setting.

D. COMPUTATIONAL STUDIES

Recent computational studies have shown that the proximal isovelocity surface area (PISA) method can quantify valvular regurgitation. The purpose of this study was to determine whether it could be applied accurately in the presence of ventricular outflow, which can distort the PISA field. Finite difference solution of the Navier-Stokes equations was therefore performed in an anatomically correct 3-dimensional ventricular model. Flow was driven through 4-6 mm diameter regurgitant orifices by a 100 mmHg pressure gradient. Each orifice size was located centrally, or near the outflow tract or posterior wall.

Regurgitant flow rates (Q) ranged from 41 to 101 ml/s. For each aliasing velocity (V) and PISA radius (R) along the centerline of the orifice, the flow rate as calculated by $Qc=2\pi R^2V$. To account for underestimation near the orifice and overestimation far from it (finite chamber and outflow effects), a polynomial was fitted to plots of Qc vs R, and Qc at the point of inflection taken as the best estimate of actual Q (least distortion). Qc at the point of inflection agreed well with actual values (mean error = 4.3 ml/s, or 6.1%), successfully accounting for potential overestimation, particularly nearest the outflow. This computational study confirms that ventricular outflow can distort adjacent PISAs, but that flow rate can still be calculated accurately by analysis of the proximal flow field in a way that could potentially be automated.

Systolic pulmonary venous (PV) flow is primarily determined by atrial pressure events. As the atrium relaxes, atrial pressure decreases and creates a favorable gradient for forward systolic flow into the atrium. However, the additional volume of regurgitation causes atrial pressure to increase rapidly and creates a pressure gradient favoring flow out of the atrium (PV flow reversal). Since the rise in pressure due to additional volume is determined by atrial compliance, we tested the hypothesis that the presence and magnitude of flow reversal is not only a function of regurgitant volume but depends on atrial compliance as well. A mathematical model of an atrium with varying compliance and PVs was developed. The atrial pressure-volume (compliance) relationship was modeled as an exponential function: initially rapidly increasing compliance (atrial relaxation) which then decreased as atrial volume increased. A simplification of the Navier-Stokes fluid flow equations was used to solve for PV velocities that result from the developed pressure gradient. Using an initial atrial volume of 40 cc (normal), the modeling was performed over a range of initial atrial compliances (C = 3-10 cc/mmHg),with and without the addition of a regurgitant jet. The model realistically simulated the systolic PV waveform in magnitude and morphology. As the volume of regurgitation increased, peak flow velocity decreased, and eventually late systolic flowreversal occurred. However, the presence andmagnitude of flow reversal was determined by atrial compliance. As the initial atrial compliance decreased, the magnitude of flow reversal increased,because higher atrial pressures were developed andpromoted flow out of the atrium into the PVs. PV flow reversal depends on atrial compliance as well as regurgitant volume. As initial atrial compliance decreases (stiffer atria), the likelihood of flow reversal increases. As a result, flow reversal is more likely in acute compared to chronic regurgitation because the atrium is less compliant.

E. EFFECT OF VALVULAR MOTION ON QUANTIFICATION OF REGURGITATION

This study addressed the hypothesis that motion of the surface containing a regurgitant orifice relative to the Doppler ultrasound transducer can cause differences between actual flow rate and calculations based on the proximal flow convergence technique. In vitro studies quantitating regurgitant flow rate by proximal flow convergence have been limited to stationary orifices. Clinically, however, valve leaflets generally move relative to the ultrasound transducer during the cardiac cycle, and can move at velocities important relative to the measured color aliasing velocities. The transducer therefore senses the vector sum of actual flow velocity toward the orifice and orifice velocity relative to the transducer. This can cause potential over- or underestimation of true flow rate depending on the direction of surface motion. The hypothesis was explored computationally and tested by pumping fluid at a constant flow rate through an orifice in a plate moving at 0-8 cm/s (velocities

comparable to those described clinically for mitral and tricuspid annular motion toward an apical transducer).

Surface motion in the same direction as flow caused overestimation of the aliasing radius and calculated flow rate. Surface motion opposite to the direction of flow (typical for mitral and tricuspid regurgitation viewed from the apex or esophagus) caused underestimation of actual flow rate; the underestimation was greater for lower aliasing velocities (36 ± 11% for 10 cm/s versus 23 ± 6% for 20 cm/s). Correcting for surface motion provided excellent agreement with actual values ($y = 0.97x + 0.10$, $r = 0.99$, SEE = 0.17 l/min). Physiologic motion of the surface containing a regurgitant orifice can cause substantial differences between actual flow rate and that calculated by the proximal flow convergence technique. Low aliasing velocities used to optimize that technique can magnify this effect. Such errors can be minimized by using higher aliasing velocities (compatible with the need to measure the aliasing radius) or eliminated by correcting for surface velocity determined by an M-mode ultrasound scan.

3. Significance

The results of our studies of the past year are providing valuable insight to cardiologists and cardiac surgeons in their efforts to non-invasively quantify valvular regurgitation using echo-Doppler techniques.

The most significant achievements during the year were:

(i) Application of fundamental engineering (fluid mechanic) principals to quantify confined and impinging valvular regurgitant jets.

(ii) Demonstrating the effects of instrument setting on assessing regurgitant jet area using transesophageal color Doppler flow mapping.

(iii) The fact that valvular motion needs to be considered when using the PISA method for quantifying regurgitant volume.

4. Plans

No changes to plans originally proposed.

(i) Continue pulsatile flow studies on central and wall jets in counter and co-flowing environments.

(ii) Continue pulsatile flow studies to test the validity of the proximal flow convergence technique to quantitate regurgitant volume.

(iii) Conduct pulsatile flow studies on prosthetic heart valves, to study the applicability of the distal jet and proximal flow convergence techniques, to quantitate prosthetic valve regurgitation.

(iv) Write journal articles based on the results of the studies conducted during the second and third years of the project.

PROGRESS REPORT SUMMARY	GR. NUMBER HL 45485-04	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR Ajit P. Yoganathan	PERIOD COVERED BY THIS REPORT FROM	THROUGH
APPLICANT ORGANIZATION Georgia Institute of Technology	01/01/93	12/31/93

TITLE OF PROJECT *(Repeat title shown in item 1 on first page)*
Quantitation of Valvular Regurgitation: An In Vitro Study

(SEE INSTRUCTIONS)

5. Human Subjects

N/A

6. Vertebrate Animals

N/A

7. Publications

A. Manuscripts

1. Cape, E. G., Levine, R. A., and Yoganathan, A. P., "Increased Heart Can Cause Underestimation of Regurgitant Jet Size by Doppler Color Flow Mapping," ***Journal of the American College of Cardiology***, vol. **21**, pp. 1029-1037, 1993.
2. Cape, E. G., Nanda, N. C., and Yoganathan, A. P., "Quantification of Regurgitant Flow Through Bileaflet Heart Valve Prostheses: Theoretical and In Vitro Studies," ***Ultrasound in Medicine and Biology***, vol. **19**, pp. 461-468, 1993.
3. Cape, E. G., Kim, Y-H., Muralidharan, E., Heinrich, R. S., Grimes, R. Y., Levine, R. A., and Yoganathan, A. P., "Cardiac Motion Can Alter Proximal Isovelocity Surface Area Calculations of Regurgitant Flow," ***Journal of the American College of Cardiology*** (In Press).
4. Walker, P. G., Kim, Y-H., Muralidharan, E., and Yoganathan, A. P., "Assessment of the Accuracy of Color Doppler Flow Mapping by Digital Image Analysis," ***Echocardiography*** (In Press).
5. Grimes, R. Y., Hopmeyer, J., Levine, R. A., and Yoganathan, A. P., "Centerline Decoy in Counterflowing Jets: Implications for Quantification of Mitral and Tricuspid Regurgitation Using Jet Centerline Velocities," ***Circulation*** (submitted).
6. Burleson, A., Fontaine, A., Levine, R. A., and Yoganathan, A. P., "A Model Based on Dimensional Analysis for Noninvasive Quantification of Valvular Regurgitation Under Confined and Impinging Conditions: In Vitro Pulsatile Flow Validation," ***Circulation*** (submitted).

B. Abstracts & Conference Presentations

1. Mele, D. Vandervort, P. M., Cape, E. G., Yoganathan, A. P., Thomas, J. D., Weyman, A. E., and Levine, R. A., "Doppler Echocardiographic Quantification of Tricuspid Regurgitation by the Momentum Method: In Vivo Validation," 65th Annual Scientific Session - American Heart Association, ***Circulation***, **86**, pp. I-253, 1992.
2. Grimes, R. Y., Walker, P. G., Nyarko, S. J., and Yoganathan, A. P., "Atrial Inflow Can Alter Color Doppler Regurgitant Jet Area: In Vitro Studies," 65th Annual Scientific Session - American Heart Association, ***Circulation***, **86**, pp. I-318, 1992.
3. Cape, E. G., Levine, R. A., Muralidharan, E., Heinrich, R., and Yoganathan, A.

P., "Increased Heartrate Can Cause Underestimation of Regurgitant Flow by Proximal Isovelocity Surface Area," 65th Annual Scientific Session - American Heart Association, ***Circulation***, **86**, pp. I-804, 1992.

4. Cape, E. G., Yoganathan, A. P. Muralidharan, E., Heinrich, R., and Levine, R. A., "Cardiac Motion Can Alter Proximal Isovelocity Surface Area Calculations of Regurgitant Flow, " 65th Annual Scientific Session - American Heart Association, ***Circulation***, **86**, pp. I-258, 1992
5. Fan, P-H., Anayitos, A., Cape, E. G., Yoganathan, A. P., and Nanda, N. C., "Intermachine Variability in Transesophegeal Color Doppler Images of Pulsatile Jets," 65th Annual Scientific Session - American Heart Association, ***Circulation***, **86**, pp. I-318, 1992.
6. Grimes, R. Y., Walker, P. G., Nyarko, S. J., Levine, R. A., and Yoganathan, A. P., "Dynamics and Quantification of Counterflowing Jets: Application to Mitral and Tricuspid Regurgitant Jets Opposed by Atrial Inflow," The Winter Annual Meeting of the American Society of Mechanical Engineers, Anaheim, CA, November 1992.
7. Cape, E. G, Muralidharan, E., Heinrich, R. S., Levine, R. A., and Yoganathan, A. P., "The Effect of Surface Motion on Proximal Isovelocity Surface Area (PISA) Calculations of Flow by Color Doppler Flow Mapping," The Winter Annual Meeting of the American Society of Mechanical Engineers, Anaheim, CA, November 1992, ***1992 Advances in Bioengineering***, pp. 435-438.
8. Grimes, R. Y., Walker, P. G., Hopmeyer, J., Yoganathan, A. P. and Levine, R. A., "Counterflowing Wall Jets are Relatively Longer than Central Jets-Implications for Regurgitant Jets Opposed by Atrial Inflow: In Vitro Studies," ***JACC***, vol. **21**, pp. 240A, 1993.
9. Grimes, R. Y., Cape, E. G., Walker, P. G., Yoganathan, A. P., and Levine, R. A., "Crossflow Augments Color Doppler Jet Area," ***JACC***, vol. **21**, pp. 367A, 1993.
10. Burleson, A. C., Mele, D., Yoganathan, A. P., Levine, R. A., "Noninvasive Quantification of Regurgitant Orifice Diameter Based on Laminar Care Length: In Vitro Laser and Ultrasound Doppler Studies," ***JACC***, vol. **21**, pp. 486A, 1993.
11. Grimes, R. Y., Levine, R. A., Yoganathan, A. P., "A New Method for Quantifying Mitral & Tricuspid Regurgitant Jets Opposed by Atrial Inflow," ***JASE***, vol. **6**, pp. S27, 1993.
12. Schwammenthal, E., Cape, E. G., Weyman, A. E., Yoganathan, A. P., Levine, R. A., "Impact of Mitral Orifice Motion in the Calculation of Regurgitant Flow Rates by the Proximal Flow Convergence Method: Clinical Data," ***JASE***, vol **6**, pp. S25, 1993.
13. Grimes, R. Y., Yang, S., Pulido, G., Levine, R. A., Yoganathan, A. P., "The Combined Effect of Atrial Walls and Inflow on Jet Dimensions," ***ASME BED***, vol. **24**, pp. 477-480, 1993.
14. Burleson, A. C., Levine, R. A., Yoganathan, A. P., "Quantification of Valvular Regurgitation: An In Vitro Study of Confined Impinging Jets," ***ASME BED*** vol. **24**, pp. 485-488, 1993.

8. Inventions and Patents

None

All Personnel for the Current Budget Period and Any Planned Changes in Personnel for the Next Budget Period

Use two sections. In the first section list *All Current Personnel*. In the second section list *Planned Personnel Changes*.

Name	Degree(s)	SSN	Role on Project *(e.g., PI, Res. Assoc.)*	Date of Birth *(MM/DD/YY)*	Annual % Effort
CURRENT PERSONNEL					
A. P. Yoganathan	Ph.D.	569-27-7875	PI	12/6/51	25
R. A. Levine	M.D.	060-46-5316	Consultant	1/29/53	7.5
A. Burleson	B.S.	255-67-3026	Grad Student	1/26/66	50
R. Grimes	M.D.	256-02-7222	Grad Student	12/27/62	100
R. Heinrich	B.S.	141-48-6193	Grad Student	1/17/69	50
J. Hopmeyer	B.S.	033-72-5382	Grad Student	3/11/69	100
F. Guenet	B.S.	252-81-8719	Grad Student	10/7/68	25
P. G. Walker	Ph.D.	252-751-226	Post Doc Fel	10/27/61	50
A. Fontaine	Ph.D.	039-34-5580	Post Doc Fel	11/19/62	75
Y. H. Kim	Ph.D.	484-11-4483	Post Doc Fel	1/19/60	25
B. Chand		382-56-7920	Secretary	11/23/52	10
PLANNED PERSONNEL CHANGES					
A. Burleson & F. Guenet, have completed their graduate studies at Georgia Tech					
No other changes are currently planned.					

Provide the number of subjects enrolled in the study *to date* according to the following categories. (See Page 8 for definitions.)

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	TOTAL
Female							
Male							
Unknown							
TOTAL							

CHECKLIST

GRANT NUMBER
HL 45485-04

Check the appropriate boxes and provide the information requested. Make this page the last page of the signed original of the application

1. ASSURANCES/CERTIFICATIONS
The following assurances/certifications are made by checking the appropriate boxes and verified by the signature of the OFFICIAL SIGNING FOR APPLICANT ORGANIZATION on the FACE PAGE of the application. Descriptions of individual assurances/certifications begin on page 9 of Specific Instructions.

a. Human Subjects *(Complete Item 7 on the Face Page)*
☐ Full IRB Review ☐ Expedited Review
Use of Human Subjects ☐ Change ☒ No Change Since Previous Submission

b. Vertebrate Animals *(Complete Item 8 on the Face Page)*
Use of Vertebrate Animals ☐ Change ☒ No Change Since Previous Submission

c. Inventions and Patents *(Complete Item 11 on the Face Page)*

d. Debarment and Suspension ☒ No ☐ Yes *(Attach explanation)*

e. Lobbying
With Federal appropriated funds ☒ No
With other than Federal appropriated funds ☒ No ☐ Yes
(If "yes", see page 13, and attach Standard Form LLL, "Disclosure of Lobbying Activities," to the application behind the Checklist.)

f. Delinquent Federal Debt ☒ No ☐ Yes *(Attach explanation)*

g. Misconduct in Science (Form PHS 6315) ☐ Filed ☒ Not Filed
If filed, date of Initial Assurance or latest Annual Report _____

h. Civil Rights	i. Handicapped Individuals	j. Sex Discrimination	k. Age Discrimination
Form HHS 441	Form HHS 641	Form HHS 639-A	Form HHS 680
☒ Filed	☒ Filed	☒ Filed	☒ Filed
☐ Not Filed	☐ Not Filed	☐ Not Filed	☐ Not Filed

2. PROGRAM INCOME *(See Instructions, Page 16)*
All applications must indicate (Yes or No) whether program income is anticipated during the period(s) for which grant support is requested. ☒ No ☐ Yes. If "Yes" use the format below to reflect the amount and source(s) of anticipated program income.

Budget Period	Anticipated Amount	Source(s)

3. INDIRECT COST
Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. Indirect costs will not be paid on foreign grants, construction grants, grants to Federal organizations and grants to individuals, and usually not on conference grants. Follow any additional instructions provided for Research Career Development Awards, Institutional National Research Service Awards, and specialized grant applications.

☐ DHHS Agreement Dated: _____ ☐ No Indirect Costs Requested
☒ No DHHS Agreement, but rates established with Office of Naval Research Date 29 June 93

CALCULATION*
Enter proposed budget period:
Amount of base $ 95051 × Rate applied 37 % = Indirect costs $ 35169
Add to total direct costs from form page 2 and enter new total on Face Page, item 10b

*Check appropriate box(es):
☐ Salary and wage base ☒ Modified total direct costs base ☐ Other base (Attach explanation)
☐ Off-site, other special rate, or more than one rate involved *(Attach explanation)*